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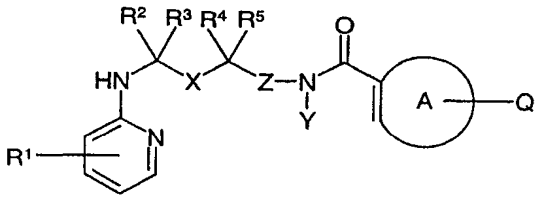

(I)

(57) Abstract

There are provided novel compounds of formula (I) wherein R^1, R^2, R^3, R^4, R^5, A, Q, X, Y, and Z are as defined in the specification, and pharmaceutically acceptable salts thereof, and enantiomers and tautomers thereof; together with processes for their preparation, compositions containing them and their use in therapy. The compounds are inhibitors of the enzyme nitric oxide synthase and are thereby particularly useful in the treatment or prophylaxis of inflammatory disease and pain.

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COMPOUNDS

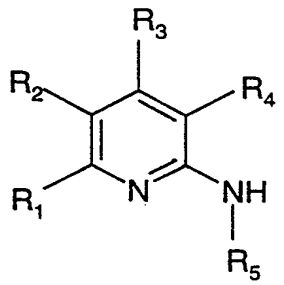
Field of the Invention

The present invention relates to novel 2-aminopyridine derivatives, processes for their preparation, compositions containing them and their use in therapy.

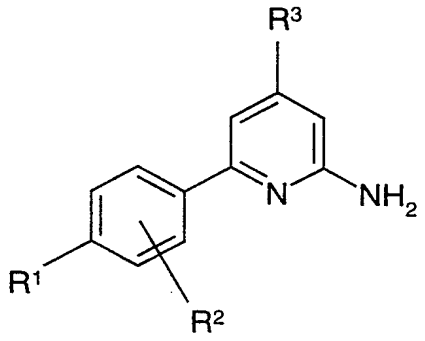
Background of the Invention

Nitric oxide is produced in mammalian cells from L-arginine by the action of specific nitric oxide synthases (NOSs). These enzymes fall into two distinct classes - constitutive NOS (cNOS) and inducible NOS (iNOS). At the present time, two constitutive NOSs and one inducible NOS have been identified. Of the constitutive NOSs, an endothelial enzyme (ecNOS) is involved with smooth muscle relaxation and the regulation of blood pressure and blood flow, whereas the neuronal enzyme (ncNOS) serves as a neurotransmitter and appears to be involved in the regulation of various biological functions such as cerebral ischaemia. Inducible NOS has been particularly implicated in the pathogenesis of inflammatory diseases. Regulation of these enzymes should therefore offer considerable potential in the treatment of a wide variety of disease states (J. E. Macdonald, *Ann. Rep. Med. Chem.*, 1996, **31**, 221 - 230).

Considerable effort has been expended in efforts to identify compounds that act as specific inhibitors of one or more isoforms of the enzyme nitric oxide synthase. The use of such compounds in therapy has also been widely claimed. One group of these compounds incorporates within their structures a 2-aminopyridine moiety. Thus, WO 96/18616 and WO 96/18617 (both to Merck & Co., Inc.) describe substituted 2-aminopyridines of general formula:



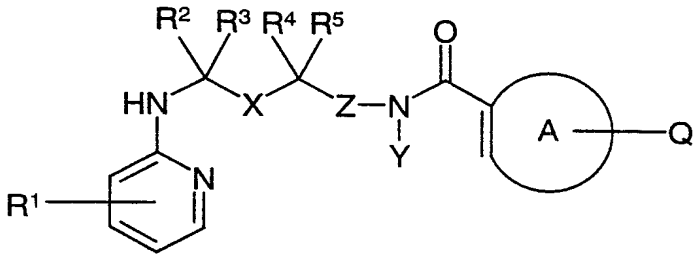
and WO 97/36871 (Pfizer Inc.) describes 6-phenyl-2-aminopyridines of general formula:



The compounds of the present invention are clearly distinguished from those of the prior art by virtue of the nature of the particular substituents attached to the 2-aminopyridine ring.

Disclosure of the invention

According to the present invention, there is provided a compound of formula (I)



(I)

wherein:

X represents $-[CR^6R^7]_n-$;

R^1 represents ~~hydrogen~~ or one or more substituents selected independently from C1 to 6 alkyl, C1 to 6 alkoxy, halogen and NR^8R^9;

R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 independently represent hydrogen or C1 to 4 alkyl;

or R^2 and R^4 are joined together and represent $-[CH_2]_m-$;

Y represents hydrogen or C1 to 4 alkyl;

or R^2 and Y are joined together and represent $-[CH_2]_p-$;

or R^4 and Y are joined together and represent $-[CH_2]_p-$;

or Y is joined to the ortho position of ring A and represents $-[CH_2]_r-$;

Z represents a bond or $-CH_2-$;

Q represents hydrogen or one or more substituents selected independently from C1 to 6 alkyl, C1 to 6 alkoxy, C1 to 6 alkylthio, halogen, cyano, trifluoromethyl, trifluoromethoxy, hydroxy, nitro, methanesulphonyl, sulphamoyl, benzyloxy, $-NR^8R^9$, $-CO_2R^{10}$, $-CONR^{11}R^{12}$, a five membered aromatic heterocyclic ring containing one to three heteroatoms independently selected from O, S or N, a six membered aromatic azacyclic ring containing one or two nitrogen atoms, or phenyl, said phenyl being optionally further substituted by C1 to 6 alkyl;

R^{10}, R^{11} and R^{12} independently represent hydrogen or C1 to 4 alkyl;

A represents phenyl, naphthyl, a five membered aromatic heterocyclic ring containing one to three heteroatoms independently selected from O, S or N, a six membered aromatic azacyclic ring containing one or two nitrogen atoms, or a bicyclic aromatic heterocyclic ring system containing one to three heteroatoms independently selected from O, S or N;

m represents an integer 0 to 5;

n represents an integer 0 to 3;

p represents an integer 0 to 4;

r represents an integer 0 to 3;

or a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof.

The compounds of formula (I) and their pharmaceutically acceptable salts, enantiomers, racemates and tautomers have the advantage that they are inhibitors of the enzyme nitric oxide synthase (NOS). In particular, the compounds of formula (I) and their pharmaceutically acceptable salts, enantiomers, racemates and tautomers have the advantage that they are inhibitors of the inducible isoform of the enzyme nitric oxide synthase (iNOS).

The invention further provides a process for the preparation of compounds of formula (I) or a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof.

According to the invention there is also provided a compound of formula (I), or a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof, for use as a medicament.

Another aspect of the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof, in the manufacture of a medicament, for the treatment or prophylaxis of diseases or conditions in which inhibition of nitric oxide synthase activity is beneficial.

A more particular aspect of the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof, in the manufacture of a medicament, for the treatment or prophylaxis of inflammatory disease.

According to the invention, there is also provided a method of treating, or reducing the risk of, diseases or conditions in which inhibition of nitric oxide synthase activity is beneficial which comprises administering to a person suffering from or at risk of, said disease or

condition, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof.

More particularly, there is also provided a method of treating, or reducing the risk of, inflammatory disease in a person suffering from or at risk of, said disease, wherein the method comprises administering to the person a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof.

The compounds of the present invention may also be used advantageously in combination with a second pharmaceutically active substance, particularly in combination with a selective inhibitor of the inducible isoform of cyclooxygenase (COX-2). Thus, in a further aspect of the invention there is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof, in combination with a COX-2 inhibitor for the treatment of inflammation, inflammatory disease and inflammatory related disorders. And there is also provided a method of treating, or reducing the risk of, inflammation, inflammatory disease and inflammatory related disorders in a person suffering from or at risk of, said disease or condition, wherein the method comprises administering to the person a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof in combination with a COX-2 inhibitor.

Preferably, A in formula (I) represents a phenyl or pyridyl ring.

Preferably, Q in formula (I) represents hydrogen, halogen or cyano.

Preferably, R^1 in formula (I) represents C1 to 6 alkyl or C1 to 6 alkoxy. More preferably, R^1 in formula (I) represents methyl or methoxy.

Preferably, n in formula (I) represents 0 or 1.

In another preferred embodiment, R^2 and Y in formula (I) are joined together and represent $-[CH_2]_2-$ and Z represents a bond and n = 1, such that R^2 and Y together with the atoms to which they are attached represent a piperidinyl ring.

Particular compounds of the invention include:

N-[1-(3-furanylcarbonyl)-4-piperidinyl]-4-methyl-2-pyridinamine;

N-[1-(4-cyanobenzoyl)-4-piperidinyl]-4-methyl-2-pyridinamine;

4-[[3-[(4-methoxy-2-pyridinyl)amino]-1-pyrrolidinyl]carbonyl]benzonitrile;

4-[[4-[(4-methoxy-2-pyridinyl)amino]-1-piperidinyl]carbonyl]benzonitrile;

N-[1-(4-bromobenzoyl)-4-piperidinyl]-4-methoxy-2-pyridinamine;

N-[1-(4-chlorobenzoyl)-4-piperidinyl]-4-methoxy-2-pyridinamine;

4-methoxy-N-[1-(2-thienylcarbonyl)-4-piperidinyl]-2-pyridinamine;

N-[1-[(5-chloro-2-thienyl)carbonyl]-4-piperidinyl]-4-methoxy-2-pyridinamine;

4-[[4-[(4-methoxy-2-pyridinyl)amino]-1-piperidinyl]carbonyl]benzenesulphonamide;

N-[1-[(6-chloro-3-pyridinyl)carbonyl]-4-piperidinyl]-4-methoxy-2-pyridinamine;

4-methoxy-N-[1-(2-pyrazinecarbonyl)-4-piperidinyl]-2-pyridinamine;

N-[1-(3,4-dichlorobenzoyl)-4-piperidinyl]-4-methoxy-2-pyridinamine;

4-methoxy-N-[1-(3-thienylcarbonyl)-4-piperidinyl]-2-pyridinamine;

4-methoxy-N-[1-(4-methoxybenzoyl)-4-piperidinyl]-2-pyridinamine;

N-[1-{(5-bromo-2-thienyl)carbonyl}-4-piperidinyl]-4-methoxy-2-pyridinamine;

4-methoxy-N-[1-{(2-(4-pyridinyl)-4-thiazolyl)carbonyl}-4-piperidinyl]-2-pyridinamine;

N-[1-(3,5-dibromobenzoyl)-4-piperidinyl]-4-methoxy-2-pyridinamine;

N-[1-(4-chloro-3-iodobenzoyl)-4-piperidinyl]-4-methoxy-2-pyridinamine;

N-[1-(3-isoqunolinylcarbonyl)-4-piperidinyl]-4-methoxy-2-pyridinamine;

4-methoxy-N-[1-(6-quinolinylcarbonyl)-4-piperidinyl]-2-pyridinamine;

N-[1-(3,5-difluorobenzoyl)-4-piperidinyl]-4-methoxy-2-pyridinamine;

4-methoxy-N-[1-[(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)carbonyl]-4-piperidinyl]-2-pyridinamine;

N-[1-[4-(dimethylamino)benzoyl]-4-piperidinyl]-4-methoxy-2-pyridinamine;

4-methoxy-N-[1-(3-quinolinylcarbonyl)-4-piperidinyl]-2-pyridinamine;

4-methoxy-N-[1-[(6-methyl-3-pyridinyl)carbonyl]-4-piperidinyl]-2-pyridinamine;

4-methoxy-N-[1-[4-(1*H*-pyrrol-1-yl)benzoyl]-4-piperidinyl]-2-pyridinamine;
N-[1-(4-iodobenzoyl)-4-piperidinyl]-4-methoxy-2-pyridinamine;
N-[1-(1-benzothiophen-2-ylcarbonyl)-4-piperidinyl]-4-methoxy-2-pyridinamine;
N-[1-[(4′-ethyl[1,1′-biphenyl]-4-yl)carbonyl]-4-piperidinyl]-4-methoxy-2-pyridinamine;
N-[1-(1*H*-1,2,3-benzotriazol-5-ylcarbonyl)-4-piperidinyl]-4-methoxy-2-pyridinamine;
4-methoxy-N-[1-[4-(1-methylethyl)benzoyl]-4-piperidinyl]-2-pyridinamine;
4-methoxy-N-[1-(1,2,3-thiadiazol-4-ylcarbonyl)-4-piperidinyl]-2-pyridinamine;
4-methoxy-N-[1-(3-pyridinylcarbonyl)-4-piperidinyl]-2-pyridinamine;
4-methoxy-N-[1-(2-pyridinylcarbonyl)-4-piperidinyl]-2-pyridinamine;
N-[1-(3-isoxazolylcarbonyl)-4-piperidinyl]-4-methoxy-2-pyridinamine;
4-methoxy-N-[1-[(5-methyl-2-pyrazinyl)carbonyl]-4-piperidinyl]-2-pyridinamine;
N-[1-[4-(aminomethyl)benzoyl]-4-piperidinyl]-4-methoxy-2-pyridinamine;
4-methoxy-N-[1-(4-pyridinylcarbonyl)-4-piperidinyl]-2-pyridinamine;
N-[1-(3-amino-4-chlorobenzoyl)-4-piperidinyl]-4-methoxy-2-pyridinamine;
N-[1-(4-cyanobenzoyl)-4-piperidinyl]-4-chloro-2-pyridinamine;
4-cyano-N-[3-[(4-methyl-2-pyridinyl)amino]propyl]benzamide;
4-cyano-N-[3-[(4-methoxy-2-pyridinyl)amino]propyl]benzamide;
N-[1-(4-chlorobenzoyl)-4-methyl-4-piperidinyl]-4-methoxy-2-pyridinamine;
and pharmaceutically acceptable salts, enantiomers, racemates or tautomers thereof.

Unless otherwise indicated, the term "C1 to 6 alkyl " referred to herein denotes a straight or branched chain alkyl group having from 1 to 6 carbon atoms or a cyclic alkyl group having from 3 to 6 carbon atoms. Examples of such groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, cyclopentyl and cyclohexyl.

Unless otherwise indicated, the term "C1 to 6 alkoxy " referred to herein denotes a straight or branched chain alkoxy group having from 1 to 6 carbon atoms. Examples of such groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy and t-butoxy.

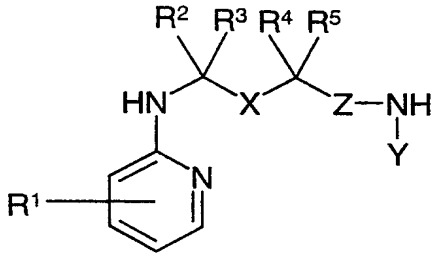
Other groups, for example, alkylthio, are to be interpreted similarly.

Examples of a five membered aromatic heterocyclic ring containing one to three heteroatoms selected independently from O, S or N, or a six membered aromatic azacyclic ring containing one or two nitrogen atoms include furan, thiophene, pyrrole, thiazole, oxazole, imidazole, triazole, thiadiazole, pyridine, pyrimidine, pyrazine and pyridazine.

Examples of a bicyclic aromatic heterocyclic ring system containing one to three heteroatoms independently selected from O, S or N include quinoline, isoquinoline, benzofuran, benzothiophene, benzothiazole, indole and benzotriazole.

According to the invention, we further provide a process for the preparation of compounds of formula (I), or a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof which comprises:

(a) preparing a compound of formula (I) by reaction of a compound of formula (II)

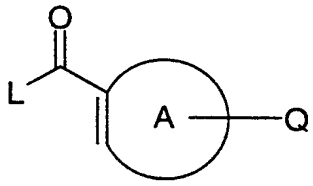


(II)

wherein

R^1, R^2, R^3, R^4, R^5, X, Y and Z are as defined above

with an acyl derivative of formula (III)

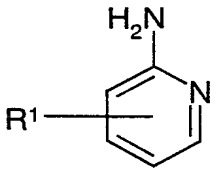


(III)

wherein

Q and A are as defined above and L represents a leaving group;

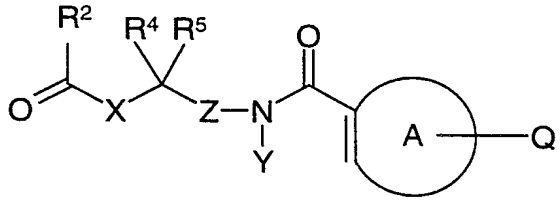
or (b) preparing a compound of formula (I) by reaction of a compound of formula (IV)



(IV)

wherein R^1 is as defined above

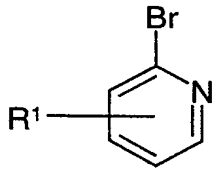
with a compound of formula (V)



(V)

wherein R^2, R^4, R^5, A, Q, X, Y and Z are as defined above;

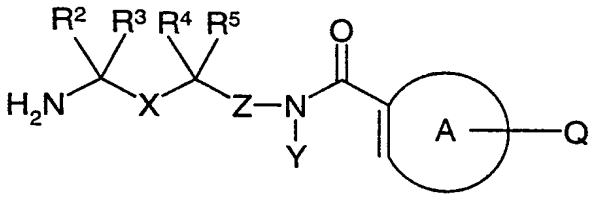
or (c) preparing a compound of formula (I) by reaction of a compound of formula (VI)



(VI)

wherein R^1 is as defined above

with a compound of formula (VII)



(VII)

wherein R^2, R^3, R^4, R^5, A, Q, X, Y and Z are as defined above;

and where desired or necessary converting the resultant compound of formula (I), or another salt thereof, into a pharmaceutically acceptable salt thereof, or *vice versa*, and where desired converting the resultant compound of formula (I) into an optical isomer thereof.

In process (a) above, the reaction will take place on stirring a mixture of the reactants in a suitable organic solvent at a suitable temperature, generally between 0 °C and the boiling point of the solvent. The reaction time will depend *inter alia* on the solvent used, the reaction temperature and the nature of the group L. The reaction may be catalysed by the addition of a base; bases that may be used include organic amines (for example, triethylamine or pyridine) and alkali metal hydroxides, alkoxides, carbonates or hydrides. Suitable leaving groups, L, include halogen (especially chlorine) and hydroxyl. When L represents OH, the reaction between compounds of formulae (II) and (III) may also be achieved using a suitable coupling agent such as CDI (1,1′-carbonyldiimidazole), DCC (1,3-dicyclohexylcarbodiimide) or HOBt (1-hydroxybenzotriazole).

In process (b) above, the reaction will take place on mixing the reactants in a suitable organic solvent in the presence of a dehydrating agent such as magnesium sulphate or aluminium oxide, or under Dean and Stark conditions, and adding a reducing agent such as sodium borohydride, sodium cyanoborohydride or sodium triacetoxyborohydride. The reaction time will depend *inter alia* on the solvent used, the reaction temperature and the nature of the group R^2.

In process (c) above, the reaction will take place on stirring a mixture of the reactants in a suitable inert organic solvent in the presence of $Pd(OAc)_2$ and (RS)-, (R)- or (S)-BINAP. Details of this process will be found in the paper by Buchwald et al, *J. Org. Chem.*, 1996, **61**, 7240.

It will be apparent to a person skilled in the art that in the above processes it may be desirable to protect an amine or other potentially reactive group. Suitable protecting groups and details of processes for adding and removing such groups may be found by reference to the standard text "Protecting Groups in Organic Synthesis", 2nd Edition (1991) by Greene and Wuts.

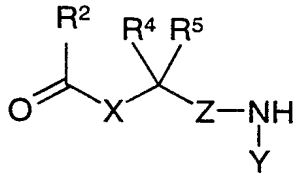
The present invention includes compounds of formula (I) in the form of salts, in particular acid addition salts. Suitable salts include those formed with both organic and inorganic

acids. Such acid addition salts will normally be pharmaceutically acceptable although salts of non-pharmaceutically acceptable acids may be of utility in the preparation and purification of the compound in question. Thus, preferred salts include those formed from hydrochloric, hydrobromic, sulphuric, phosphoric, citric, tartaric, lactic, pyruvic, acetic, succinic, fumaric, maleic, methanesulphonic and benzenesulphonic acids.

Salts of compounds of formula (I) may be formed by reacting the free base, or a salt, enantiomer, racemate or tautomer thereof, with one or more equivalents of the appropriate acid. The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, for example, water, dioxane, ethanol, tetrahydrofuran or diethyl ether, or a mixture of solvents, which may be removed *in vacuo* or by freeze drying. The reaction may also be a metathetical process or it may be carried out on an ion exchange resin.

Certain novel intermediates of formulae (II), (III), (V) and (VII) form another aspect of the invention.

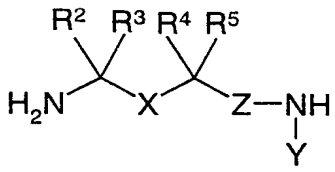
The preparation of compounds of formula (II) may be achieved by reaction of a compound of formula (IV) with a compound of formula (VIII)



(VIII)

using the methodology of process (b) above.

Alternatively, the preparation of compounds of formula (II) may be achieved by reaction of a compound of formula (VI) with a compound of formula (IX)



(IX)

using the methodology of process (c) above.

Methods for the preparation of compounds of formulae (III), (IV), (V), (VI), (VII), (VIII) and (IX) are either known *per se* or may be achieved using methods that are well known in the art.

Intermediate compounds may be used in protected form. Protecting groups and details of processes for their removal may be found by reference to the standard text "Protecting groups in Organic Synthesis", 2nd Edition (1991) by Greene and Wuts.

The compounds of the invention and intermediates thereto may be isolated from their reaction mixtures and, if necessary further purified, by using standard techniques.

The compounds of formula I may exist in enantiomeric forms. Therefore, all enantiomers, diastereomers, racemates and mixtures thereof are included within the scope of the invention. The various optical isomers may be isolated by separation of a racemic mixture of the compounds using conventional techniques, for example, fractional crystallisation, or HPLC.

Intermediate compounds may also exist in enantiomeric forms and may be used as purified enantiomers, diastereomers, racemates or mixtures.

The compounds of formula (I) may exist in alternative tautomeric forms. Compounds of formula (I) are provided in another tautomeric form or as a mixture thereof.

The compounds of formula (I), and their pharmaceutically acceptable salts, enantiomers, racemates and tautomers, are useful because they possess pharmacological activity in animals. In particular, the compounds are active as inhibitors of the enzyme nitric oxide synthase. More particularly, they are inhibitors of the inducible isoform of the enzyme nitric oxide synthase and as such are predicted to be useful in therapy, for example, as anti-inflammatory

agents. They may also have utility as inhibitors of the neuronal isoform of the enzyme nitric oxide synthase.

The compounds and their pharmaceutically acceptable salts, enantiomers, racemates and tautomers are indicated for use in the treatment or prophylaxis of diseases or conditions in which synthesis or oversynthesis of nitric oxide synthase forms a contributory part. In particular, the compounds are indicated for use in the treatment of inflammatory conditions in mammals including man.

Conditions that may be specifically mentioned are:
osteoarthritis, rheumatoid arthritis, rheumatoid spondylitis, gouty arthritis and other arthritic conditions, inflamed joints;
eczema, psoriasis, dermatitis or other inflammatory skin conditions such as sunburn;
inflammatory eye conditions including uveitis and conjunctivitis;
lung disorders in which inflammation is involved, for example, asthma, bronchitis, chronic obstructive pulmonary disease, pigeon fancier's disease, farmer's lung, acute respiratory distress syndrome;
bacteraemia, endotoxaemia (septic shock), aphthous ulcers, gingivitis, pyresis, pain, meningitis and pancreatitis;
conditions of the gastrointestinal tract including inflammatory bowel disease, Crohn's disease, atrophic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, peptic ulceration, irritable bowel syndrome, damage to the gastrointestinal tract resulting from infections by, for example, *Helicobacter pylori*, or from treatments with non-steroidal anti-inflammatory drugs;
and other conditions associated with inflammation.

The compounds will also be useful in the treatment and alleviation of acute pain or persistent inflammatory pain or neuropathic pain or pain of a central origin.

We are particularly interested in the conditions inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, chronic obstructive pulmonary disease and pain.

The compounds of formula (I) and their pharmaceutically acceptable salts, enantiomers, racemates and tautomers may also be useful in the treatment or prophylaxis of diseases or conditions in addition to those mentioned above. For example, the compounds may be useful in the treatment of atherosclerosis, glaucoma, cystic fibrosis, hypotension associated with septic and/or toxic shock, in the treatment of dysfunction of the immune system, as an adjuvant to short-term immunosuppression in organ transplant therapy, in the control of onset of diabetes, in the maintenance of pancreatic function in diabetes, in the treatment of vascular complications associated with diabetes and in cotherapy with cytokines, for example TNF or interleukins.

The compounds of formula (I) may also be useful in the treatment of hypoxia, for example in cases of cardiac arrest and stroke, neurodegenerative disorders including nerve degeneration and/or nerve necrosis in disorders such as ischaemia, hypoxia, hypoglycaemia, epilepsy, and in external wounds (such as spinal cord and head injury), hyperbaric oxygen convulsions and toxicity, dementia, for example pre-senile dementia, Alzheimer's disease and AIDS-related dementia, Sydenham's chorea, Parkinson's disease, Tourette's Syndrome, Huntington's disease, Amyotrophic Lateral Sclerosis, Multiple Sclerosis, Korsakoff's disease, imbecility relating to a cerebral vessel disorder, sleeping disorders, schizophrenia, depression, pain, autism, seasonal affective disorder, jet-lag, depression or other symptoms associated with Premenstrual Syndrome (PMS), anxiety and septic shock. Compounds of formula (I) may also be expected to show activity in the prevention and reversal of tolerance to opiates and diazepines, treatment of drug addiction, treatment of migraine and other vascular headaches, neurogenic inflammation, in the treatment of gastrointestinal motility disorders, cancer and in the induction of labour.

We are particularly interested in the conditions stroke, Alzheimer's disease, Parkinson's disease, multiple sclerosis, schizophrenia, migraine, cancer, septic shock and pain.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the disease or condition in question. Persons at risk of developing a particular disease or

condition generally include those having a family history of the disease or condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

For the above mentioned therapeutic indications, the dosage administered will, of course, vary with the compound employed, the mode of administration and the treatment desired. However, in general, satisfactory results are obtained when the compounds are administered at a dosage of the solid form of between 1 mg and 2000 mg per day.

The compounds of formula (I), and pharmaceutically acceptable derivatives thereof, may be used on their own, or in the form of appropriate pharmaceutical compositions in which the compound or derivative is in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier. Administration may be by, but is not limited to, enteral (including oral, sublingual or rectal), intranasal, intravenous, topical or other parenteral routes. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, "Pharmaceuticals - The Science of Dosage Form Designs", M. E. Aulton, Churchill Livingstone, 1988. The pharmaceutical composition preferably comprises less than 80% and more preferably less than 50% of a compound of formula (I), or a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof.

There is also provided a process for the preparation of such a pharmaceutical composition that comprises mixing the ingredients.

The compounds of formula (I), and pharmaceutically acceptable derivatives thereof, may also be advantageously used in combination with a COX-2 inhibitor. Particularly preferred COX-2 inhibitors are Celecoxib and MK-966. The NOS inhibitor and the COX-2 inhibitor may either be formulated together within the same pharmaceutical composition for administration in a single dosage unit, or each component may be individually formulated such that separate dosages may be administered either simultaneously or sequentially.

The invention is illustrated, but in no way limited, by the following examples:

Intermediate A

4-[(4-Methyl-2-pyridinyl)amino]-1-piperidinecarboxylic acid ethyl ester

2-Bromo-4-methylpyridine (1.72 g, 0.01 moles), palladium acetate (0.11 g, 0. 5 mmol), racemic BINAP (0.31 g, 0.5 mmol), 4-amino-1-ethoxycarbonylpiperidine (2.0 ml, 12 mmol) and potassium tert-butoxide (1.57 g, 14 mmol) were heated in toluene (50 ml) at 70 °C for 4 h. The cooled solution was diluted with water, extracted with ethyl acetate, the extracts washed with brine, dried (magnesium sulphate) and evaporated. The residue was purified by flash column chromatography eluting with ethyl acetate to yield the title compound as a solid (2.3 g, 88%).

MS (+CI) ^{m}/z 264 ($[M+H]^{+}$).

Intermediate B

4-Methyl-N-(4-piperidinyl)-2-pyridinamine

4-[(4-Methyl-2-pyridinyl)amino]-1-piperidinecarboxylic acid ethyl ester (2.2 g, 8.4 mmol) (Intermediate A) was dissolved in ethanol (50 ml) and water (25 ml). Sodium hydroxide (48% w/v, 25 ml) was added and the solution was refluxed for 20 h, cooled and extracted with ethyl acetate. The residue was purified by flash column chromatography eluting with 5% methanol in dichloromethane to yield the title compound as an oil (1.5 g).

MS (+CI) ^{m}/z 192 ($[M+H]^{+}$).

Intermediate C

4-[(4-Methoxy-2-pyridinyl)amino]-1-piperidinecarboxylic acid ethyl ester

This was prepared by the same procedure used for Intermediate A, but using 2-chloro-4-methoxypyridine, to give the title compound as a brown oil.

MS (+CI) ^{m}/z 280 ($[M+H]^{+}$).

Intermediate D

4-Methoxy-N-(4-piperidinyl)-2-pyridinamine

This was prepared by the same procedure used for Intermediate B, but using 4-[(4-methoxy-2-pyridinyl)amino]-1-piperidinecarboxylic acid ethyl ester (Intermediate C), to give the title compound as an off-white solid.

MS (+CI) ^{m}/z 208 ($[M+H]^{+}$).

Intermediate E

4-Methoxy-N-[1-(phenylmethyl)-3-pyrrolidinyl]-2-pyridinamine

A mixture of 2-bromo-4-methylpyridine (5.76 mmol, 986 mg), 1-(phenylmethyl)-3-pyrrolidinamine (1.12 g, 1.1 equivalents), racemic BINAP (180 mg, 5 mol%), palladium acetate (65 mg), potassium tert-butoxide (903 mg) in toluene (30 ml) was heated to 70 °C for 16h, cooled, diluted with water and extracted three times with ethyl acetate. The combined extracts were dried over sodium sulphate and evaporated. The residue was purified by flash column chromatography eluting with 5-10% methanol in dichloromethane to yield the title compound as a yellow oil (700 mg).

MS (+CI) ^{m}/z 268 ($[M+H]^{+}$).

Intermediate F

N-(4-Methoxy-2-pyridyl)pyrrolidin-3-amine

4-Methoxy-N-[1-(phenylmethyl)-3-pyrrolidinyl]-2-pyridinamine (700 mg, 2.62 mmol), palladium hydroxide (350 mg), cyclohexene (35 ml) and ethanol (70 ml) were heated to reflux for 16h, cooled and filtered through celite. Evaporation gave the title compound as a yellow oil (464 mg).

MS (+CI) ^{m}/z 178 ($[M+H]^{+}$).

Intermediate G

N′-(4-Methyl-2-pyridinyl)-1,3-propanediamine

A mixture of palladium acetate (106 mg), racemic BINAP (291 mg) and 2-bromo-4-methylpyridine (9.63 mmol, 1.07 ml) was heated in toluene (66 ml) to 70 °C for 20 min., propane-1,3-diamine (1.00 ml, 12 mmol) and sodium tert-butoxide (1.11 g) were added, and the mixture heated for a further 3 h. After cooling, the solution was diluted with water, extracted four times with ethyl acetate, these extracts discarded, and extraction continued with dichloromethane (six times). The dichloromethane extracts were combined, dried over sodium sulphate and evaporated to give the amine as a yellow oil which solidified on standing.

MS (+CI) ^{m}/z 166 ($[M+H]^{+}$).

Intermediate H

N′-(4-Methoxy-2-pyridinyl)-1,3-propanediamine

This was prepared using the same method as for Intermediate G but starting with 4-methoxy-2-chloropyridine to afford the title compound as a yellow oil.

MS (+CI) ^{m}/z 183 ($[M+H^{+}]$).

Intermediate I

4-[(4-Chloro-2-pyridinyl)amino]-1-piperidinecarboxylic acid ethyl ester

This was prepared by the same method as for Intermediate A but using 2,4-dichloropyridine to afford the title compound as a yellow oil.

MS (+CI) ^{m}/z 284/286 ($[M+H]^{+}$).

Intermediate J

4-Chloro-N-(4-piperidinyl)-2-pyridinamine

This was prepared by the same method as for Intermediate B but using 4-[(4-chloro-2-pyridinyl)amino]-1-piperidinecarboxylic acid ethyl ester to afford the title compound as a yellow oil.

MS (+CI) $^{m}/z$ 212/214 ($[M+H]^{+}$).

Intermediate K

1-(4-Chlorobenzoyl)-4-methylenepiperidine

Methyl phosphonium bromide (7.1 g, 0.02 mol) was suspended in tetrahydrofuran (75 ml) and 2M butyl lithium (10 ml in hexane, 0.02 mol) added at 0 °C. After 1 h at room temperature the solution was added dropwise over 30 min. to a solution of 1-(4-chlorobenzoyl)-4-piperidone (2.38 g, 0.01 mol) in tetrahydrofuran (75 ml). After 16 h, water was added, followed by extraction with ether three times. The extracts were combined, dried over magnesium sulphate and evaporated. The residue was purified by flash column chromatography eluting with 30% ethyl acetate in hexane to yield the title compound as an oil.

MS (+EI) $^{m}/z$ 236/238 (M^{+}).

Intermediate L

4-Azido-1-(4-chlorobenzoyl)-4-methylpiperidine

Sodium azide (0.5 g, 7.65 mmol) was added to 1-(4-chlorobenzoyl)-4-methylenepiperidine (0.6 g, 2.6 mmol) in tetrahydrofuran/water (1:1, 10 ml) followed by mercuric acetate (0.83 g, 2.6 mmol). The mixture was heated to 90 °C for 24 h, cooled to 0 °C, and 1N aqueous sodium hydroxide (6.8 ml) added, followed by sodium borohydride (50 mg, 1.4 mmol) in 1N aqueous sodium hydroxide over 5 minutes. Stirring was continued for

20 min., then the mixture was extracted with ether twice, dried over magnesium sulphate and evaporated. The residue was purified by flash column chromatography eluting with 30% ethyl acetate in hexane to yield the title compound as an oil.

MS (+CI) ^{m}/z 279/281 ($[M+H]^{+}$).

Intermediate M

1-(4-Chlorobenzoyl)-4-methyl-4-piperidinamine

4-Azido-1-(4-chlorobenzoyl)-4-methylpiperidine (0.31 g, 1.1 mmol) and triphenylphosphine (0.32 g, 1.2 mmol) were refluxed in 33% aqueous dioxane for 24h. The reaction mixture was evaporated, diluted with dilute hydrochloric acid and extracted with ethyl acetate. The acid layer was basified with aqueous potassium carbonate, extracted with dichloromethane three times, the combined dichloromethane layers dried over magnesium sulphate and evaporated to give the title compound as an oil (0.23 g).

MS (+CI) ^{m}/z 253/255 ($[M+H]^{+}$).

Example 1

N-[1-(3-Furanylcarbonyl)-4-piperidinyl]-4-methyl-2-pyridinamine

A mixture of 4-methyl-N-(4-piperidinyl)-2-pyridinamine (0.19 g, 1 mmol) (Intermediate B), 3-furancarboxylic acid (0.12 g, 1.1 mmol), bromo-tris-pyrrolidinophosphonium hexafluorophosphate (0.7 g, 1.5 mmol) and Hunig's base (0.52 ml, 3 mmol) was stirred in dichloromethane for 20 h. The solution was diluted with water, separated and the organic layer dried (magnesium sulphate) and evaporated. The residue was purified by flash column chromatography eluting with ethyl acetate to yield the product, which was dissolved in ethanol, 4N hydrochloric acid in dioxane added and the solution evaporated. Trituration with ether gave the title compound as the hydrochloride salt (0.18 g).

MS (+CI) ^{m}/z 286 ($[M+H]^{+}$);

300MHz ^{1}H NMR (d_6-DMSO) 8.66 (1H, br.s), 8.06 (1H, s), 7.83 (1H, d), 7.76 (1H, s), 6.90 (1H, s), 6.74 (1H, d), 6.67 (1H, s), 3.99-3.97 (1H, m), 3.64-3.58 (1H, m), 3.2-3.0 (3H, m), 2.34 (3H, s), 1.99 (2H, d), 1.43 (2H, ddd).

Example 2

N-[1-(4-Cyanobenzoyl)-4-piperidinyl]-4-methyl-2-pyridinamine

A mixture of 2-amino-4-methylpyridine (1.01 g, 9.4 mmol) and 1-(4-cyanobenzoyl)piperidin-4-one (1.35 g, 9.4 mmol) were heated neat to 120 °C for 4 h. The reaction mixture was then cooled to 40-50 °C, and tetrahydrofuran was cautiously added to dissolve the mixture. Sodium borohydride (0.39 g, 10 mmol) was added at room temperature and stirring continued for 16 h, then dilute aqueous hydrochloric acid was added, followed by solid sodium bicarbonate. After extraction with ethyl acetate, the organic extracts were dried over sodium sulphate and evaporated. The residue was purified by flash column chromatography eluting with 2% methanol in dichloromethane to yield the title compound as a golden oil (0.09 g).

MS (+CI) $^{m}/z$ 321 ($[M+H]^{+}$);

300MHz ^{1}H NMR (d_6-DMSO) 7.94 (2H, d), 7.8 (1H, d), 7.56 (2H, d), 6.3 (2H, m), 4.32 (1H, m), 3.96 (1H, m), 3.44 (1H, m), 3.18-3.06 (2H, m), 2.12 (3H, s), 1.99-1.82 (2H, m).

Example 3

4-[[3-[(4-Methoxy-2-pyridinyl)amino]-1-pyrrolidinyl]carbonyl]benzonitrile

4-Cyanobenzoic acid chloride (160 mg, 0.963 mmol) was added with stirring to a solution of N-(4-methoxy-2-pyridyl)pyrrolidin-3-amine (155 mg, 0.876 mmol) and triethylamine (0.3 ml) in dichloromethane. After 1 h, the solution was diluted with water, extracted twice with dichloromethane and the combined extracts dried over sodium sulphate and evaporated. The residue was purified by flash column chromatography eluting with 2 - 4% methanol in dichloromethane to yield the title compound as a colourless film which was treated with 1N HCl in diethyl ether to precipitate a white solid of the title compound hydrochloride salt.

MS (+CI) $^{m}/z$ 307 ($[M+H]^{+}$);

400MHz ^{1}H NMR (d_6-DMSO) (a 1:1 mixture of rotamers) 13.48 (1H, br.s), 9.13 (0.5H, br.s), 8.96 (0.5H, br.s), 7.97-7.92 (2H, m), 7.88 (0.5H, d), 7.80 (0.5H, d), 7.72 (2H, d), 6.95

(0.5H, s), 6.87 (0.5H, s), 6.79 (0.5H, d), 6.75 (0.5H, d), 4.47 (0.5H, br.s), 4.39 (0.5H, br.s), 3.86-3.81 (1H, m), 3.65-3.3 (3H, m), 2.36 (1.5H, s), 2.32 (1.5H, s), 2.4-2.2 (1H, m), 2.03-2.96 (1H, s).

Example 4

4-[[4-[(4-Methoxy-2-pyridinyl)amino]-1-piperidinyl]carbonyl]benzonitrile

A solution of 4-cyanobenzoic acid (148 mg, 1 mmol) in N,N-dimethylformamide (4 ml) was treated with carbonyldiimidazole (196 mg, 1.2 mmol). After stirring for 30 minutes, 4-methoxy-N-(4-piperidinyl)-2-pyridinamine (1 mmol) in N,N-dimethylformamide (2 ml) was added. After a further 30 min, the solution was diluted with water, extracted three times with ethyl acetate, the combined extracts dried (sodium sulphate), evaporated and purified by normal phase HPLC eluting with 0 - 10% ethanol/dichloromethane to yield, after trituration with diethyl ether, a white solid (177 mg).

MS (+CI) ^{m}/z 337 ($[M+H]^{+}$);

300MHz ^{1}H NMR (d_6-DMSO) 7.95 (2H, d), 7.84 (1H, d), 7.61 (2H, d), 6.55 (1H, dd), 6.45 (1H, s), 4.4 (1H, br.s), 4.0 (1H, br.s), 3.91 (1H, br.s), 3.5 (1H, br.s), 3.2 (1H, br.s), 3.15-3.0 (1H, br.m), 2.1-2.0 (1H, br.m), 1.95-1.85 (2H, br.m), 1.55 (2H, br.m).

Following the general method of Example 4 but using the acid stated, the compounds of Examples 5 to 39 were prepared.

Example 5

N-[1-(4-Bromobenzoyl)-4-piperidinyl]-4-methoxy-2-pyridinamine

Using 4-bromobenzoic acid. The hydrochloride salt of the title compound was obtained as a white solid after trituration with 1N HCl in ether.

MS (+CI) ^{m}/z 391 ($[M+H]^{+}$);

400MHz ^{1}H NMR (d_6-DMSO) 8.53 (1H, br.s), 7.84 (1H, d), 7.66 (2H, d), 7.38 (2H, d), 6.54 (1H, dd), 6.44 (1H, s), 4.2 (1H, br.s), 3.98-3.96 (1H, br.d),), 3.70 (3H, s), 3.6 (1H, br.s), 3.2- 3.0 (2H, br.s), 2.05 -1.95 (2H, br.m), 1.5-1.4 (2H, br.s).

Example 6

N-[1-(4-Chlorobenzoyl)-4-piperidinyl]-4-methoxy-2-pyridinamine

Using 4-chlorobenzoic acid. A white solid.

MS (+CI) $^{m}/z$ 347 ($[M+H]^{+}$);

400MHz ^{1}H NMR (d_6-DMSO) 7.77 (1H, d, J 6Hz), 7.52 (1H, d, J 8Hz), 7.41 (1H, d, J 8Hz), 6.38 (1H, d, J 6.8Hz), 6.13-6.11 (1H, m), 5.98 (1H, s), 4.4-4.2 (1H, br.m), 4.0-3.9 (1H, br.m), 3.70 (3H, s), 3.6-3.5 (1H, br.m), 3.2-3.0 (2H, br.m), 2.0-1.8 (2H, br.m), 1.4-1.3 (2H, br.m).

Example 7

4-Methoxy-N-[1-(2-thienylcarbonyl)-4-piperidinyl]-2-pyridinamine

Using 2-thiophenecarboxylic acid. A white powder.

MS (+CI) $^{m}/z$ 318 ($[M+H]^{+}$);

400MHz ^{1}H NMR (d_6-DMSO) 7.77 (1H, d, J 6Hz), 7.75 (1H, d, J 6Hz), 7.39-7.38 (1H, m), 7.12 (1H, dd, J 3.6, 4.8Hz), 6.40 (1H, d, J 8Hz), 6.13-6.11 (1H, m), 5.98 (1H, s), 4.18 (2H, br.s), 4.00 (1H, s), 3.70 (3H, s), 3.20 (1H, br.s), 1.95 (2H, d, J 9Hz), 1.42-1.32 (2H, m).

Example 8

N-[1-[(5-Chloro-2-thienyl)carbonyl]-4-piperidinyl]-4-methoxy-2-pyridinamine

Using 2-(5-chloro)thiophenecarboxylic acid. A white powder.

MS (+CI) $^{m}/z$ 352 ($[M+H]^{+}$);

400MHz ^{1}H NMR (d_6-DMSO) 7.78 (1H, d), 7.30 (1H, d), 7.15 (1H, d), 6.40 (1H, d), 6.11 (1H, dd), 5.98 (1H, d), 4.15 (2H, d), 4.01-3.99 (1H, br.m), 3.70 (3H, s), 1.95 (1h, dm), 1.37 (1H, dd).

Example 9

4-[[4-[(4-Methoxy-2-pyridinyl)amino]-1-piperidinyl]carbonyl]benzenesulphonamide

Using 4-sulphonamidobenzoic acid. A white powder.

MS (+CI) ^{m}/z 391 ($[M+H]^{+}$);

400MHz ^{1}H NMR (d_6-DMSO) 7.88 (2H, d, J 8.4Hz), 7.77 (1H, d, J 6Hz), 7.57 (2H, d, J 8.4Hz), 7.45 (2H, s), 6.38 (1H, d, J 7.6Hz), 6.11 (1H, dd, J 2.4, 6Hz), 5.98 (1H, s), 4.34 (1H, br.s), 3.98 (1H, br.s), 3.70 (3H, s), 3.5-3.4 (1H, br.m), 3.2-3.0 (2H, br.m), 2-1.8 (2H, m), 1.4-1.2 (2H, m).

Example 10

N-[1-[(6-Chloro-3-pyridinyl)carbonyl]-4-piperidinyl]-4-methoxy-2-pyridinamine

Using 6-chloronicotinic acid. A white powder.

MS (+CI) ^{m}/z 347 ($[M+H]^{+}$);

400MHz ^{1}H NMR (d_6-DMSO) 8.46 (1H, s), 7.90 (1H, dd), 7.77 (1H, d), 7.63 (1H, d), 6.38 (1H, d), 6.12 (1H, dd), 5.98 (1H, s), 4.29 (1H, br.s), 3.99-3.96 (1H, m), 3.70 (3H, s), 3.52 (1H, br.s), 3.30-3.0 (2H, br.m), 2.0-1.8 (2H, m), 1.5-1.3 (2H, m).

Example 11

4-Methoxy-N-[1-(2-pyrazinecarbonyl)-4-piperidinyl]-2-pyridinamine

Using pyrazine carboxylic acid. A white powder.

MS (+CI) ^{m}/z 314 ($[M+H]^{+}$);

400MHz ^{1}H NMR (d_6-DMSO) 8.30 (1H, s), 8.74 (1H, s), 8.67 (1H, s), 7.77 (1H, d), 6.41 (1H, d), 6.12 (1H, dd), 5.97 (1H, s), 4.35 (1H, d), 4.02-4.01 (1H, m), 3.71 (3H, s), 3.70-3.64 (1H, m), 3.22 (1H, dt), 3.10 (1H, dt), 2.01 (1H, br.d), 1.86 (1H, br.d), 1.39 (1H, dq).

Example 12

N-[1-(3,4-Dichlorobenzoyl)-4-piperidinyl]-4-methoxy-2-pyridinamine

Using 3,4-dichlorobenzoic acid. A white solid.

MS(+ CI) ^{m}/z 380/382 ($[M + H]^{+}$);

300MHz ^{1}H NMR (d_6 - DMSO) 7.77 (1H, d, J 6Hz), 7.72 (1H, d, J 8Hz), 7.66 (1H, d, J 2Hz), 7.38 (1H, dd, J 8Hz, J 2Hz), 6.37 (1H, d, J 7.5Hz), 6.12 (1H, dd, J 6Hz, J 2Hz), 5.98 (1H, d, J2Hz), 4.29 (1H, br.m), 3.97 (1H, br.m), 3.12 (2H, br.m), 1.92 (2H, br.m), 1.36 (2H, br.m)

Example 13

4-Methoxy-N-[1-(3-thienylcarbonyl)-4-piperidinyl]-2-pyridinamine

Using thiophene-3-carboxylic acid. A white solid.

MS(+ CI) ^{m}/z 318 ($[M+H]^{+}$);

300 MHz ^{1}H NMR (d_6 - DMSO) 7.76 (2H, m), 7.61 (1H, m), 7.19 (1H, dd, J 5Hz, J 1Hz), 6.38 (1H, d, J 8Hz), 6.12 (1H, dd, J 6Hz, J 2Hz), 5.98 (1H, d, J 2Hz), 4.2 (1H, br.m), 3.99 (2H, br.m), 3.7 (3H, s), 3.1 (2H, br.m) 1.92 (2H, br.d), 1.34 (2H, br.m)

Example 14

4-Methoxy-N-[1-(4-methoxybenzoyl)-4-piperidinyl]-2-pyridinamine

Using 4-methoxybenzoic acid. A white solid.

MS(+ CI) ^{m}/z 342 ($[M + H]^{+}$);

300MHz ^{1}H NMR (d_6-DMSO) 7.77 (1H, d, J 6Hz), 7.35 (2H, d, J 9Hz), 6.99 (2H, d, J 9Hz), 6.37 (1H, d, J 8Hz), 6.11 (1H, dd, J 6Hz, J 2Hz), 5.97 (1H, d, J 2Hz), 4.2 (1H, br.m), 3.97 (2H, br.m), 3.79 (3H, s), 3.70 (3H, s), 3.09 (2H, br.m), 1.90 (2H, br.m), 1.33 (2H, br.m).

Example 15

N-[1-{(5-Bromo-2-thienyl)carbonyl}-4-piperidinyl]-4-methoxy-2-pyridinamine

Using 5-bromothiophene-2-carboxylic acid. A white solid.

MS(+CI) ^{m}/z 396/398 ($[M + H]^{+}$);

300MHz ^{1}H NMR (d_6-DMSO) 7.78 (1H, d, J 6Hz), 7.25 (2H, s), 6.40 (1H, d, J 8Hz), 6.12 (1H, dd, J 6Hz, J 2Hz), 5.98 (1H, d, J 2Hz), 4.14 (2H, br.d), 4.02 (1H, br.m), 3.71 (3H, s), 3.21 (2H, br.m), 1.95 (2H, br.m), 1.37 (2H, br.m).

Example 16

4-Methoxy-N-[1-{(2-(4-pyridinyl)-4-thiazolyl)carbonyl}-4-piperidinyl]-2-pyridinamine

Using 2-(pyridin-4-yl)thiazole-4-carboxylic acid. A pale yellow solid.

MS(+CI) ^{m}/z 396 ($[M+H]^{+}$);

300 MHz ^{1}H NMR (d_6-DMSO) 8.74 (2H, dd, J 4.5Hz, J 1.5Hz), 8.30 (1H, s), 7.92 (2H, dd, J 4.5Hz, J 1.5Hz), 7.78 (1H, d, J 6Hz), 6.43 (1H, d, J 8Hz), 6.13 (1H, dd, J 6Hz, J 2Hz), 5.98 (1H, d, J 2Hz), 4.37 (1H, br.m), 4.08 (2H, br.m), 3.71 (3H, s), 3.33 (1H, br.m), 3.08 (1H, br.m), 1.99 (2H, br.m), 1.44 (2H, br.m).

Example 17

N-[1-(3,5-Dibromobenzoyl)-4-piperidinyl]-4-methoxy-2-pyridinamine

Using 3,5-dibromobenzoic acid. A white solid.

MS(+CI) ^{m}/z 468/470/472 ($[M+H]^{+}$);

300MHz ^{1}H NMR (d_6-DMSO) 7.94 (1H, t, J 2Hz), 7.77 (1H, d, J 6Hz), 7.61 (2H, d, J 2Hz), 6.36 (1H, d, J 8Hz), 6.12 (1H, dd, J 6Hz, J 2Hz), 5.98 (1H, d, J 2Hz), 4.26 (1H, br.m), 3.96 (1H, br.m), 3.71 (3H, s), 3.46 (1H, br.m), 3.19 (1H, br.m), 3.04 (1H, br.m), 1.96 (1H, br.m), 1.88 (1H, br.m), 1.36 (2H, br.m).

Example 18

N-[1-(4-Chloro-3-iodobenzoyl)-4-piperidinyl]-4-methoxy-2-pyridinamine

Using 4-chloro-3-iodobenzoic acid. A white solid.

MS(+CI) ^{m}/z 472/474 ($[M+H]^{+}$);

300MHz ^{1}H NMR (d_6-DMSO) 7.92 (1H, d, J 2Hz), 7.77 (1H, d, J 6Hz), 7.65 (1H, d, J 8Hz), 7.42 (1H, dd, J 8Hz, J 2Hz), 6.37 (1H, d J 8Hz), 6.12 (1H, dd, J 6Hz, J 2Hz), 5.98 (1H, d, J 2Hz), 4.27 (1H, br.m), 3.95 (1H, br.m), 3.70 (3H, s), 3.51 (1H, br.m), 3.12 (2H, br.m), 1.92 (2H, br.m), 1.36 (2H, br.m).

Example 19

N-[1-(3-Isoquinolinylcarbonyl)-4-piperidinyl]-4-methoxy-2-pyridinamine

Using 3-isoquinoline carboxylic acid. A white solid.

MS (+CI) ^{m}/z 363 ($[M+H]^{+}$);

300MHz ^{1}H NMR (d_6-DMSO) 9.34 (1H, s), 8.20 (1H, d, J 8Hz), 8.08 (2H, m), 7.86 (1H, t), 7.77 (2H, m), 6.43 (1H, d, J 8Hz), 6.12 (1H, dd, J 6Hz, J 2Hz), 5.98 (1H, d, J 2Hz), 4.42 (1H, br.d), 4.02 (1H, br.m), 3.76 (1H, br.m), 3.71 (3H, s), 3.24 - 3.06 (2H, m), 2.03 (1H, br.m), 1.85 (1H, br.m), 1.42 (2H, br.m).

Example 20

4-Methoxy-N-[1-(6-quinolinylcarbonyl)-4-piperidinyl]-2-pyridinamine

Using 6-quinolinecarboxylic acid. A white solid.

MS (+CI) ^{m}/z 363 ($[M+H]^{+}$);

300MHz ^{1}H NMR (d_6-DMSO) 8.9 (1H, d, J 3Hz), 8.46 (1H, d, J 8Hz), 8.05 (2H, m), 7.76 (2H, m), 7.61 (1H, m), 6.41 (1H, d, J 8Hz), 6.12 (1H, dd, J 6Hz, J 2Hz), 5.99 (1H, d, J 2Hz), 4.39 (1H, br.m), 4.01 (1H, br.m), 3.71 (3H, s), 3.65 (1H, br.m), 3.2 (2H, br.m), 1.95 (2H, br.m), 1.41 (2H, br.m).

Example 21

N-[1-(3,5-Difluorobenzoyl)-4-piperidinyl]-4-methoxy-2-pyridinamine

Using 3,5-difluorobenzoic acid. A white solid.

MS(+CI) ^{m}/z 348 ($[M+H]^{+}$);

300MHz ^{1}H NMR(d_6-DMSO) 7.77 (1H, d, J 6Hz), 7.35 (1H, t of t), 7.15 (2H, m), 6.37 (1H, d, J 8Hz), 6.12 (1H, dd, J 6Hz,J 2Hz), 5.98 (1H, d, J 2Hz), 4.28 (1H, br.m), 3.95 (1H, br.m), 3.70 (3H, s), 3.39 (1H, br.m), 3.11 (2H, br.m), 1.91 (2H, br.m), 1.36 (2H, br.m).

Example 22

4-Methoxy-N-[1-[(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)carbonyl]-4-piperidinyl]-2-pyridinamine

Using 5-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic acid. A white solid.

MS (+CI) ^{m}/z 392 ($[M+H]^{+}$);

400MHz ^{1}H NMR (d_6-DMSO) 7.78 (1H, d, J 6Hz), 7.75 (1H, s), 7. 58-7.45 (5H, m), 6.39 (1H, d, J 8Hz), 6.13-6.11 (1H, m), 5.98 (1H, d, J 2Hz), 4.25-3.8 (3H, m), 3.71 (3H, s), 3.15 (2H, br.m), 2.35 (3H, s), 1.97-1.94 (2H, m), 1.41-1.31 (2H, m).

Example 23

N-[1-[4-(Dimethylamino)benzoyl]-4-piperidinyl]-4-methoxy-2-pyridinamine

Using 4-dimethylaminobenzoic acid. A white solid.

MS (+CI) ^{m}/z 355 ($[M+H]^{+}$);

400MHz ^{1}H NMR (d_6-DMSO) 7.77 (1H, d, J 6Hz), 7.26 (2H, d, J 9Hz), 6.71 (2H, d, J 9Hz), 6.37 (1H, d, J 8Hz), 6.11 (1H, dd, J 8Hz, J 2Hz), 5.96 (1H, d, J 2Hz), 4.1-3.9 (3H, br.m), 3.7 (3H, s), 3.08 (2H, br.m), 2.94 (6H, s), 1.9 (2H, m), 1.32 (2H, m).

Example 24

4-Methoxy-N-[1-(3-quinolinylcarbonyl)-4-piperidinyl]-2-pyridinamine

Using quinoline-3-carboxylic acid. A white solid.

MS(+CI) ^{m}/z 363 ($[M+H]^{+}$);

400MHz ^{1}H NMR (d_6-DMSO) 8.91 (1H, d, J 2Hz), 8.45 (1H, d, J 2Hz), 8.09-8.06 (2H, m), 7.87-7.83 (1H, m), 7.77 (1H, d, J 6Hz), 7.71-7.67 (1H, m), 6.41 (1H, d, J 8Hz), 6.12 (1H, dd, J 8Hz, J 2Hz), 6.0 (1H, d, J 2Hz), 4.39 (1H, br. m), 4.02 (1H, br.m), 3.71 (3H, s), 3.66 (1H, br.m), 3.4-3.1 (2H, br.m), 2.0-1.9 (2H, br.m), 1.44 (2H, br.m).

Example 25

4-Methoxy-N-[1-[(6-methyl-3-pyridinyl)carbonyl]-4-piperidinyl]-2-pyridinamine

Using 6-methylpyridine-3-carboxylic acid. A white solid.

MS(+CI) ^{m}/z 327 ($[M+H]^{+}$);

400MHz ^{1}H NMR (d_6-DMSO) 8.46 (1H, t, J 1Hz), 7.77 (1H, d, J 6Hz), 7.7 (1H, dd, J 7Hz, J 2Hz) 7.33 (1H, d, J 8Hz), 6.38 (1H, d, J 8Hz), 6.12 (1H, dd, J 6Hz, J 2Hz), 5.98 (1H, d, J 2.4Hz), 4.31 (1H, br.m), 3.98 (1H, br.m), 3.7 (3H, s), 3.55 (1H, br.m), 3.3-3.0 (2H, br.m), 2.5 (3H, s), 2.0-1.8 (2H, br.m), 1.36 (2H, br.m).

Example 26

4-Methoxy-N-[1-[4-(1*H*-pyrrol-1-yl)benzoyl]-4-piperidinyl]-2-pyridinamine

Using 4-(1*H*-pyrrol-1-yl) benzoic acid. A white solid.

MS (+CI) ^{m}/z 377 ($[M+H]^{+}$);

400MHz ^{1}H NMR (d_6-DMSO) 7.77 (1H, d, J 6Hz), 7.66 (2H, d, J 8Hz), 7.47 (2H, d, J 8Hz), 7.44-7.43 (2H, m), 6.38 (1H, d, J 8Hz), 6.3 (2H, m), 6.12 (1H, dd, J 6Hz, J 2Hz), 5.98 (1H, d, J 2Hz), 4.3 (1H, br.m), 4.0 (1H, br.m), 3.7 (3H, s), 3.66 (1H, br.m), 3.13 (2H, br.m), 1.97 (2H, br.m), 1.37 (2H, br.m).

Example 27

N-[1-(4-Iodobenzoyl)-4-piperidinyl]-4-methoxy-2-pyridinamine

Using 4-iodobenzoic acid. A white solid.

MS (+CI) ^{m}/z 438 ($[M+H]^{+}$);

400MHz ^{1}H NMR (d_6-DMSO) 7.83-7.81 (2H, m), 7.77 (1H, d, J 6Hz), 7.2-7.17 (2H, m), 6.37 (1H, d, J 8Hz), 6.13-6.1 (1H, m), 5.97 (1H, d, J 2Hz), 4.3 (1H, br.m), 4.0-3.94 (1H, m), 3.7 (3H, s), 3.52 (1H, br.m), 3.2-3.3 (2H, br.m), 2-1.8 (2H, br.m), 1.4-1.2 (2H, br.m).

Example 28

N-[1-(1-Benzothiophen-2-ylcarbonyl)-4-piperidinyl]-4-methoxy-2-pyridinamine

Using 1-benzothiophene-2-carboxylic acid. A white solid.

MS(+CI) ^{m}/z 368 ($[M+H]^{+}$);

400MHz ^{1}H NMR (d_6-DMSO) 8.03-8.01 (1H, m), 7.95-7.93 (1H, m), 7.78 (1H, d, J 6Hz), 7.08 (1H, s), 7.47-7.42 (2H, m), 6.42 (1H, d, J 8Hz), 6.14-6.12 (1H, m), 5.99 (1H, d, J 2Hz), 4.21 (2H, br.m), 4.03 (1H, m), 3.7 (3H, s), 3.25 (2H, br.m), 2-1.97 (2H, m), 1.47-1.37 (2H, br.m).

Example 29

N-[1-[(4′-Ethyl[1,1′-biphenyl]-4-yl)carbonyl]-4-piperidinyl]-4-methoxy-2-pyridinamine

Using 4′-ethyl[1,1′-biphenyl]-4-carboxylic acid. A white solid.

MS(+CI) ^{m}/z 416 ($[M+H]^{+}$);

400MHz ^{1}H NMR (d_6-DMSO) 7.77 (1H, d, J 6Hz), 7.72 (2H, dd, J 6Hz, J 2Hz), 7.62 (2H, dd, J 6Hz, J 2Hz), 7.46 (2H, dd, J 6Hz, J 2Hz), 7.32 (2H, d, J 8Hz), 6.39 (1H, d, J 7Hz), 6.12 (1H, dd, J 6Hz, J 2Hz), 5.98 (1H, d, J 2Hz), 4.34 (1H, br.m), 4.0 (1H, br.m), 3.7 (3H, s), 3.65 (1H, br.m), 3.3-3 (2H, br.m), 2.65 (2H, q, J 8Hz), 1.37 (2H, br.m), 1.22 (3H, t, J 8Hz).

Example 30

N-[1-(1*H*-1,2,3-Benzotriazol-5-ylcarbonyl)-4-piperidinyl]-4-methoxy-2-pyridinamine

Using 1*H*-1,2,3-benzotriazole-5-carboxylic acid. A white solid.

MS(+CI) ^{m}/z 353 ($[M+H]^{+}$);

400MHz ^{1}H NMR (d_6-DMSO) 7.93 (1H, d, J 9Hz), 7.9 (1H, s), 7.77 (1H, d, J 6Hz), 7.38 (1H, dd, J 8Hz, J 1Hz), 6.4 (1H, d, J 8Hz), 6.11 (1H, dd, J 6Hz, J 2Hz), 6.0 (1H, d, J 2Hz), 4.0 (1H, br.m), 3.7 (3H, s), 3.6-3.1 (4H, br.m), 1.9 (2H, br.m), 1.4 (2H, br.m).

Example 31

4-Methoxy-N-[1-[4-(1-methylethyl)benzoyl]-4-piperidinyl]-2-pyridinamine

Using 4-(1-methylethyl)-benzoic acid. A white solid.

MS(+CI) ^{m}/z 354 ($[M+H]^{+}$);

400MHz ^{1}H NMR (d_6-DMSO) 7.77 (1H, d, J 6Hz), 7.33-7.29 (4H, m), 6.37 (1H, d, J 8Hz), 6.11 (1H, dd, J 6Hz, J 2Hz), 5.97 (1H, d, J 2Hz), 4.3 (1H, br.m), 3.98 (1H, br.m), 3.7 (3H, s), 3.6 (1H, br.m), 3.1 (1H, br.m), 2.92 (1H, quin), 1.9 (2H, br.m), 1.3 (2H, br.m), 1.23 (6H, d, J 7Hz).

Example 32

4-Methoxy-N-[1-(1,2,3-thiadiazol-4-ylcarbonyl)-4-piperidinyl]-2-pyridinamine

Using 1,2,3-thiadiazole-4-carboxylic acid. The hydrochloride salt of the title compound was obtained as a white solid.

MS(+CI) ^{m}/z 320 ($[M+H]^{+}$);

300MHz ^{1}H NMR (d_6-DMSO) 13.02 (NH, br.s), 9.57 (1H, s), 8.54 (NH, br.s), 7.86-7.84 (1H, d), 6.55-6.52 (1H, dd), 6.45-6.44 (1H, d), 4.51-4.46 (1H, d), 4.03 (1H, m), 3.91 (3H, s), 3.39 (2H), 3.16-3.11 (1H), 2.99 (1H, d), 1.95 (1H,d), 1.58-1.48 (2H, m).

Example 33

4-Methoxy-N-[1-(3-pyridinylcarbonyl)-4-piperidinyl]-2-pyridinamine

Using nicotinic acid. A white solid.

MS(+CI) ^{m}/z 313 ($[M+H)^{+}$];

300MHz ^{1}HNMR (d_6-DMSO) 8.65-8.63 (1H, dd), 8.60-8.59 (1H, dd), 7.84-7.80 (1H), 7.78-7.76 (1H, d), 7.50-7.46 (1H, m), 6.39-6.37 (1H,d), 6.13-6.10 (1H, dd), 5.98-5.97 (1H, d), 4.31 (1H, br.s), 3.99-3.94 (1H, m), 3.70 (3H, s), 3.57-3.51 (1H, m), 3.07 (2H, m), 1.99-1.89 (2H, m), 1.38 (2H, br.s).

Example 34

4-Methoxy-N-[1-(2-pyridinylcarbonyl)-4-piperidinyl]-2-pyridinamine

Using picolinic acid. A white solid.

MS(+CI) ^{m}/z 313 ($[M+H]^{+}$);

300MHz ^{1}H NMR (d_6-DMSO) 8.59-8.57 (1H,m), 7.95-7.89 (1H, m), 7.77-7.76 (1H, d), 7.55-7.52 (1H, d), 7.49-7.45 (1H, q), 6.41-6.38 (NH, d), 6.12-6.10 (1H, dd), 5.97-5.96 (1H, d), 4.37-4.33 (1H, br.d), 4.01-3.99 (1H, m), 3.70 (3H, s), 3.65-3.61 (1H, d), 3.19-3.01 (2H, m), 2.01-1.82 (2H, m), 1.43-1.32 (2H, br.q).

Example 35

N-[1-(3-Isoxazolylcarbonyl)-4-piperidinyl]-4-methoxy-2-pyridinamine

Using 3-isoxazolecarboxylic acid. A white solid.

MS(+CI) ^{m}/z 303 ($[M+H]^{+}$);

300MHz ^{1}HNMR (d_6-DMSO) 9.08-9.07 (1H, d), 7.78-7.76 (1H, d), 6.81-6.81 (1H, d), 6.42-6.39 (NH, d), 6.13-6.11 (1H, dd), 5.97-5.96 (1H, d), 4.34-4.30 (1H, m), 4.03-4.01(1H, m), 3.85-3.80 (1H, m), 3.70 (3H, s), 3.23-3.22 (1H, m), 3.14-3.05 (1H, m), 2.01-1.89 (2H, m), 1.42-1.30 (2H, m).

Example 36

4-Methoxy-N-[1-[(5-methyl-2-pyrazinyl)carbonyl]-4-piperidinyl]-2-pyridinamine

Using 5-methyl-2-pyrazine carboxylic acid. A white solid.

MS(+CI) ^{m}/z 328 ($[M+H]^{+}$);

300MHz ^{1}HNMR (d_6-DMSO) 8.69-8.68 (1H, d), 8.56-8.55 (1H, d), 7.78-7.76 (1H, d), 6.41-6.39 (NH, d), 6.13-6-6.10 (1H, dd), 5.97-5.96 (1H, d), 4.36-4.32 (1H, br.d), 4.02-3.99 (1H, m), 3.70 (3H, s), 3.25-3.04 (2H, m), 2.55 (3H, s), 2.02-1.99 (1H, m), 1.87-1.84 (1H, m), 1.44-1.34 (2H, m).

Example 37

N-[1-[4-(Aminomethyl)benzoyl]-4-piperidinyl]-4-methoxy-2-pyridinamine

Using 4-(9-fluorenylmethoxycarbonyl)aminomethyl)benzoic acid together with the following work-up procedure. The reaction mixture was diluted with water and ethyl acetate and the organic layer was washed with 2M hydrochloric acid. The aqueous layer was extracted three times with ethyl acetate. The aqueous layer was then concentrated down and the golden oil obtained was purified via super critical fluid chromatography. This gave the title compound as a white solid.

MS(+CI) ^{m}/z 341 ($[M+H]^{+}$);

300MHz ^{1}H NMR (d6-DMSO) 7.86-7.77 (1H, d), 7.39-7.41 (2H, d), 7.35-7.32 (2H, d), 6.38-6.35 (1H, d), 6.12-6.10 (1H, dd), 5.97-5.96 (1H, d), 4.30-4.28 (1H, m), 3.99 (1H, m), 3.79 (2H, s), 3.70 (3H, s), 3.56 (1H, m), 3.18 (2H, m), 1.89 (2H, m), 1.24 (2H, m).

Example 38

4-Methoxy-N-[1-(4-pyridinylcarbonyl)-4-piperidinyl]-2-pyridinamine

Using isonicotinic acid. A white solid.

MS(+CI) 313 ($[M+H]^{+}$);

300MHz ^{1}H NMR (d_6-DMSO) 8.69-8.67 (2H, d), 7.84-7.81 (1H, d), 7.40-7.38 (2H, dd), 6.44-6.42 (1H, d), 6.28 (1H, s), 6.10 (2H, s), 4.40-4.37 (1H, m), 3.85 (3H, s), 3.32 (3H), 2.04-1.86 (2H, m), 1.44-1.41 (2H, m).

Example 39

N-[1-(3-Amino-4-chlorobenzoyl)-4-piperidinyl]-4-methoxy-2-pyridinamine

Using 3-amino-4-chlorobenzoic acid. A white solid.

MS(+CI) ^{m}/z 361 ($[M+H]^+$);

300MHz ^{1}H NMR (d_6-DMSO) 7.77-7.75 (1H, d), 7.24-7.21 (1H, d), 6.77-6.77 (1H, d), 6.51-6.48 (1H, dd), 6.38-6.36 (1H, d), 6.12-6.10 (1H, dd), 5.97-5.96 (1H, d), 5.53 (2H, s), 4.3 (1H, m), 3.95 (1H, m), 3.56 (1H, m), 3.06 (2H, m), 1.90 (2H, m), 1.30 (2H, m).

Example 40

N-[1-(4-Cyanobenzoyl)-4-piperidinyl]-4-chloro-2-pyridinamine

The title compound was prepared using the method of Example 3 and starting with 4-chloro-N-(4-piperidinyl)-2-pyradinamine (Intermediate J) and 4-cyanobenzoic acid chloride. The free base was isolated as a white solid.

MS(+ CI) ^{m}/z 342/345 ($[M + H]^+$);

400MHz ^{1}H NMR (d_6-DMSO) 7.95-7.92 (3H, m), 7.58 (2H, d), 6.81 (1H, d), 6.54-6.52 (2H, m), 4.38-4.26 (1H, br.m), 4.04-3.95 (1H, br.m), 3.5-3.4 (1H, br.m), 3.2-3.0 (2H, br.m), 2.05-1.8 (2H, br.m), 1.5-1.2 (2H, br.m).

Example 41

4-Cyano-N-[3-[(4-methyl-2-pyridinyl)amino]propyl]benzamide

4-Cyanobenzoyl chloride (163 mg, 0.98 mmol) was added to a solution of N′-(4-methyl-2-pyridinyl)-1,3-propanediamine (Intermediate G) (162 mg, 0.98 mmol) and triethylamine (0.5 ml) in dichloromethane (20 ml). After 1 h, the solution was diluted with water,

extracted with ethyl acetate, the extract dried over sodium sulphate and evaporated. Purification by column chromatography on silica gel eluting with 3% methanol/dichloromethane gave the title compound as a white solid (130 mg).

MS (+CI) ^{m}/z 295 ($[M+H]^{+}$);

300MHz ^{1}H NMR (d_6-DMSO) 8.75 (1H, t, J 5.2Hz), 8.00-7.95 (4H, m), 7.80 (1H, d, J 5.2Hz), 6.36 (1H, t, J 5.6Hz), 6.30 (1H, d, J 5.2Hz), 6.25 (1H, s), 3.36-3.24 (4H, m), 2.12 (3H, s), 1.76 (1H, pentet, J 7.2Hz).

Example 42

4-Cyano-N-[3-[(4-methoxy-2-pyridinyl)amino]propyl]benzamide

The title compound was prepared using the method of Example 42 and starting with N′-(4-methoxy-2-pyridinyl)-1,3-propanediamine (Intermediate H) as a yellow solid.

MS (+CI) ^{m}/z 312 ($[M+H]^{+}$);

400MHz ^{1}H NMR (d_6-DMSO) 8.76 (1H, t), 8.01-7.94 (4H, apparent dd), 7.76 (1H, d), 6.40 (1H, t), 6.11 (1H, dd), 5.95 (1H, d), 3.70 (1H, t), 6.11 (1H, dd), 5.95 (1H, d), 3.70 (3H, s), 3.37-3.24 (4H, m), 1.76 (2H, pentet).

Example 43

N-[1-(4-Chlorobenzoyl)-4-methyl-4-piperidinyl]-4-methoxy-2-pyridinamine

The title compound was prepared from 1-(4-chlorobenzoyl)-4-methyl-4-piperidinamine (Intermediate M) and 2-chloro-4-methoxypyridine using the method of Intermediate A. The hydrochloride salt was obtained as a white solid.

MS(+CI) ^{m}/z 360/363 ($[M+H]^{+}$);

400MHz ^{1}H NMR (d_6-DMSO) 8.42 (1H, br.s), 7.97 (1H, d), 7.51 (2H, d), 7.44 (2H, d), 6.57 (1H, d), 6.48 (1H, s), 4.05-4.0 (1H, br.m), 3.93 (3H, s), 3.5-3.3 (3H, m), 2.3-1.8 (2H, m), 1.8-1.7 (2H, br.m), 1.48 (3H, s).

Screens

The pharmacological activity of compounds according to the invention was tested in the following screens.

Screen 1

The activity of compounds of formula (I), or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, may be screened for nitric oxide synthase inhibiting activity by a procedure based on that of Förstermann *et al.*, Eur. J. Pharm., 1992, **225**, 161-165. Nitric oxide synthase converts ^{3}H-L-arginine into ^{3}H-L-citrulline which can be separated by cation exchange chromatography and quantified by liquid scintillation counting.

Enzyme is prepared, after induction, from the cultured murine macrophage cell line J774A-1 (obtained from the laboratories of the Imperial Cancer Research Fund). J774A-1 cells are cultured in Dulbeccos Modified Eagles Medium (DMEM) supplemented with 10% foetal bovine serum, 4 mM L-glutamine and antibiotics (100 units/ml penicillin G, 100 mg/ml streptomycin & 0.25 mg/ml amphotericin B). Cells are routinely grown in 225 cm^3 flasks containing 35 ml medium kept at 37 °C and in a humidified atmosphere containing 5% CO_2.

Nitric oxide synthase is produced by cells in response to interferon-g (IFNg) and lipopolysaccharide (LPS). The medium from confluent culture flasks is removed and replaced with 25 ml (per flask) of fresh medium containing 1 mg/ml LPS and 10 units/ml IFNg. After a period of 17-20 hours in culture, harvesting of cells is accomplished by scraping the cell sheet from the flask surface into the culture medium. Cells are collected by centrifugation (1000 g for 10 minutes) and lysate prepared by adding to the cell pellet a solution containing 50 mM Tris-HCl (pH 7.5 at 20 °C), 10% (v/v) glycerol, 0.1% (v/v) Triton-X-100, 0.1 mM dithiothreitol and a cocktail of protease inhibitors comprising leupeptin (2 mg/ml), soya bean trypsin inhibitor (10 mg/ml), aprotinin (5 mg/ml) and phenylmethylsulphonyl fluoride (50 mg/ml).

For the assay, 25 µl of substrate cocktail (50 mM Tris-HCl (pH 7.5 at 20 °C), 400 µM NADPH, 20 µM flavin adenine dinucleotide, 20 µM flavin mononucleotide, 4 µM

tetrahydrobiopterin, 12 μM L-arginine and 0.025 mCi L-[^{3}H] arginine) is added to wells of a 96 well filter plate (0.45μM pore size) containing 25 μl of a solution of test compound in 50 mM Tris-HCl. The reaction is started by adding 50 μl of cell lysate (prepared as above) and after incubation for 1 hour at room temperature is terminated by addition of 50 μl of an aqueous solution of 3 mM nitroarginine and 21 mM EDTA.

Labelled L-citrulline is separated from labelled L-arginine using Dowex AG-50W. 150 μl of a 25% aqueous slurry of Dowex 50W (Na^+ form) is added to the assay after which the whole is filtered into 96 well plates. 75 μl of filtrate is sampled and added to wells of 96 well plates containing solid scintillant. After allowing the samples to dry the L-citrulline is quantified by scintillation counting.

In a typical experiment basal activity is 300 dpm per 75 μl sample which is increased to 1900 dpm in the reagent controls. Compound activity is expressed as IC_{50} (the concentration of drug substance which gives 50% enzyme inhibition in the assay) and aminoguanidine, which gives an IC_{50} (50% inhibitory concentration) of 10 μM, is tested as a standard to verify the procedure. Compounds are tested at a range of concentrations and from the inhibitions obtained IC_{50} values are calculated. Compounds that inhibit the enzyme by at least 25% at 100 μM are classed as being active and are subjected to at least one retest.

In the above screen, the compounds of Examples 1 to 43 were tested and gave IC_{50} values of less than 25 μM indicating that they are expected to show useful therapeutic activity.

Screen 2

Compounds also show activity against the human form of induced nitric oxide synthase as can be demonstrated in the following assay.

Enzyme is prepared, after induction, from the cultured human colon adrenocarcinoma cell line DLD1 (obtained from the European Collection of Animal Cell Culture - cell line number 90102540). DLD1 cells are cultured in RPMI 1640 medium supplemented with

10% foetal bovine serum, 4 mM L-glutamine and antibiotics (100 units/ml penicillin G, 100 µg/ml streptomycin and 0.25 µg/ml amphotericin B). Cells are routinely grown in 225 cm^3 flasks containing 35 ml medium kept at 37 °C and in a humidified atmosphere containing 5% CO_2.

Nitric oxide synthase is produced by cells in response to interferon-γ (IFN-γ) and interleukin-1β (IL-1β). The medium from confluent flasks is removed and replaced with 25 ml (per flask) of fresh medium containing 250 units/ml IL-1β and 1000 units/ml IFN-γ. After a period of 17–20 hours in culture, harvesting of cells is accomplished by scraping the cell monolayer from the flask surface into the culture medium. Cells are collected by centrifugation (1000g for 10 minutes) and lysate prepared by adding to the cell pellet a solution containing 50 mM Tris-HCl (pH 7.5 at 20°C), 10% (v/v) glycerol, 0.1% (v/v) Triton-X100, 0.1 mM dithiothreitol and a cocktail of protease inhibitors including leupeptin (2 µg/ml), soya bean trypsin inhibitor (10 µg/ml), aprotonin (5 µg/ml) and phenylmethylsulphonyl fluoride (50 µg/ml).

For the assay, 25 µl of substrate cocktail (50 mM Tris-HCl (pH 7.5), 400 µM NADPH, 20 µM flavin adenine dinucleotide, 20 µM flavin mononucleotide and 4 µM tetrahydrobiopterin) is added to the wells of a 96-well plate. Test compounds are preincubated with enzyme by adding together with 40 µl of cell lysate (prepared as above) and incubating for 1 hour at 37 °C at the end of which period 10 µl of 30 µM L-arginine and 0.025 µCi of L-[^{3}H]-arginine in 50 mM Tris-HCl is added to start the enzymatic reaction. Incubation is continued for a further 1 hour at 37 °C. The reaction is terminated by addition of 50 µl of an aqueous solution of 3 mM nitroarginine and 21 mM EDTA.

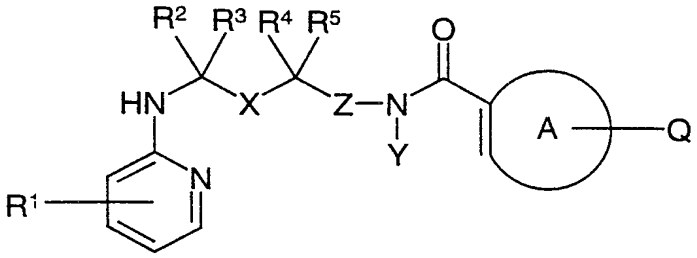
Labelled L-citrulline is separated from labelled L-arginine using Dowex AG-50W. 120 µl of a 25% aqueous slurry of Dowex 50W is added to 96 well filter plates (0.45 µm pore size). To this is added 120 µl of terminated assay mix. 75 µl of filtrate is sampled and added to the wells of 96 well plates containing solid scintillant. After allowing the samples to dry the L-citrulline is quantified by scintillation counting.

In a typical experiment basal activity is 300 dpm per 75 µl sample of reagent controls, which is increased to 3000 dpm in the presence of enzyme. Compound activity is expressed as IC_{50} (the concentration of drug substance which gives 50% enzyme inhibition in the assay) and L-NMMA, which gives an IC_{50} of about 0.4 µM is tested as a standard to verify the procedure. Compounds are tested at a range of concentrations and from the inhibitions obtained IC_{50} values are calculated.

In this screen the compounds of Examples 1 to 43 gave IC_{50} values of less than 25 µM, indicating that they are predicted to show useful therapeutic activity.

CLAIMS:

1. A compound of formula (I)



(I)

wherein

X represents $-[CR^6R^7]_n-$;

R^1 represents hydrogen or one or more substituents selected independently from C1 to 6 alkyl, C1 to 6 alkoxy, halogen and NR^8R^9;

R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 independently represent hydrogen or C1 to 4 alkyl;

or R^2 and R^4 are joined together and represent $-[CH_2]_m-$;

Y represents hydrogen or C1 to 4 alkyl;

or R^2 and Y are joined together and represent $-[CH_2]_p-$;

or R^4 and Y are joined together and represent $-[CH_2]_p-$;

or Y is joined to the ortho position of ring A and represents $-[CH_2]_r-$;

Z represents a bond or $-CH_2-$;

Q represents hydrogen or one or more substituents selected independently from C1 to 6 alkyl, C1 to 6 alkoxy, C1 to 6 alkylthio, halogen, cyano, trifluoromethyl, trifluoromethoxy, hydroxy, nitro, methanesulphonyl, sulphamoyl, benzyloxy, $-NR^8R^9$, $-CO_2R^{10}$, $-CONR^{11}R^{12}$, a five membered aromatic heterocyclic ring containing one to three heteroatoms independently selected from O, S or N, a six membered aromatic azacyclic ring containing one or two nitrogen atoms, or phenyl, said phenyl being optionally further substituted by C1 to 6 alkyl;

R^{10}, R^{11} and R^{12} independently represent hydrogen or C1 to 4 alkyl;

A represents phenyl, naphthyl, a five membered aromatic heterocyclic ring containing one to three heteroatoms independently selected from O, S or N, a six membered aromatic azacyclic ring containing one or two nitrogen atoms, or a bicyclic aromatic heterocyclic ring system containing one to three heteroatoms independently selected from O, S or N;

m represents an integer 0 to 5;

n represents an integer 0 to 3;

p represents an integer 0 to 4;

r represents an integer 0 to 3;

or a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof.

2. A compound of formula (I), according to Claim 1, wherein A represents a phenyl or pyridyl ring.

3. A compound of formula (I), according to Claim 1 or Claim 2, wherein R^1 represents C1 to 6 alkyl or C1 to 6 alkoxy.

4. A compound of formula (I), according to any one of Claims 1 to 3, wherein Q represents hydrogen, halogen or cyano.

5. A compound of formula (I), according to any one of Claims 1 to 4, wherein n represents 0 or 1.

6. A compound of formula (I), according to any one of Claims 1 to 5, wherein R^2 and Y in formula (I) are joined together and represent $-[CH_2]_2-$ and Z represents a bond and n = 1, such that R^2 and Y together with the atoms to which they are attached represent a piperidinyl ring.

7. A compound of formula (I) which is:
N-[1-(3-furanylcarbonyl)-4-piperidinyl]-4-methyl-2-pyridinamine;
N-[1-(4-cyanobenzoyl)-4-piperidinyl]-4-methyl-2-pyridinamine;
4-[[3-[(4-methoxy-2-pyridinyl)amino]-1-pyrrolidinyl]carbonyl]benzonitrile;
4-[[4-[(4-methoxy-2-pyridinyl)amino]-1-piperidinyl]carbonyl]benzonitrile;
N-[1-(4-bromobenzoyl)-4-piperidinyl]-4-methoxy-2-pyridinamine;
N-[1-(4-chlorobenzoyl)-4-piperidinyl]-4-methoxy-2-pyridinamine;
4-methoxy-N-[1-(2-thienylcarbonyl)-4-piperidinyl]-2-pyridinamine;
N-[1-[(5-chloro-2-thienyl)carbonyl]-4-piperidinyl]-4-methoxy-2-pyridinamine;
4-[[4-[(4-methoxy-2-pyridinyl)amino]-1-piperidinyl]carbonyl]benzenesulphonamide;
N-[1-[(6-chloro-3-pyridinyl)carbonyl]-4-piperidinyl]-4-methoxy-2-pyridinamine;
4-methoxy-N-[1-(2-pyrazinecarbonyl)-4-piperidinyl]-2-pyridinamine;
N-[1-(3,4-dichlorobenzoyl)-4-piperidinyl]-4-methoxy-2-pyridinamine;
4-methoxy-N-[1-(3-thienylcarbonyl)-4-piperidinyl]-2-pyridinamine;
4-methoxy-N-[1-(4-methoxybenzoyl)-4-piperidinyl]-2-pyridinamine;
N-[1-{(5-bromo-2-thienyl)carbonyl}-4-piperidinyl]-4-methoxy-2-pyridinamine;

4-methoxy-N-[1-{(2-(4-pyridinyl)-4-thiazolyl)carbonyl}-4-piperidinyl]-2-pyridinamine;
N-[1-(3,5-dibromobenzoyl)-4-piperidinyl]-4-methoxy-2-pyridinamine;
N-[1-(4-chloro-3-iodobenzoyl)-4-piperidinyl]-4-methoxy-2-pyridinamine;
N-[1-(3-isoqunolinylcarbonyl)-4-piperidinyl]-4-methoxy-2-pyridinamine;
4-methoxy-N-[1-(6-quinolinylcarbonyl)-4-piperidinyl]-2-pyridinamine;
N-[1-(3,5-difluorobenzoyl)-4-piperidinyl]-4-methoxy-2-pyridinamine;
4-methoxy-N-[1-[(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)carbonyl]-4-piperidinyl]-2-pyridinamine;
N-[1-[4-(dimethylamino)benzoyl]-4-piperidinyl]-4-methoxy-2-pyridinamine;
4-methoxy-N-[1-(3-quinolinylcarbonyl)-4-piperidinyl]-2-pyridinamine;
4-methoxy-N-[1-[(6-methyl-3-pyridinyl)carbonyl]-4-piperidinyl]-2-pyridinamine;
4-methoxy-N-[1-[4-(1*H*-pyrrol-1-yl)benzoyl]-4-piperidinyl]-2-pyridinamine;
N-[1-(4-iodobenzoyl)-4-piperidinyl]-4-methoxy-2-pyridinamine;
N-[1-(1-benzothiophen-2-ylcarbonyl)-4-piperidinyl]-4-methoxy-2-pyridinamine;
N-[1-[(4′-ethyl[1,1′-biphenyl]-4-yl)carbonyl]-4-piperidinyl]-4-methoxy-2-pyridinamine;
N-[1-(1*H*-1,2,3-benzotriazol-5-ylcarbonyl)-4-piperidinyl]-4-methoxy-2-pyridinamine;
4-methoxy-N-[1-[4-(1-methylethyl)benzoyl]-4-piperidinyl]-2-pyridinamine;
4-methoxy-N-[1-(1,2,3-thiadiazol-4-ylcarbonyl)-4-piperidinyl]-2-pyridinamine;
4-methoxy-N-[1-(3-pyridinylcarbonyl)-4-piperidinyl]-2-pyridinamine;
4-methoxy-N-[1-(2-pyridinylcarbonyl)-4-piperidinyl]-2-pyridinamine;
N-[1-(3-isoxazolylcarbonyl)-4-piperidinyl]-4-methoxy-2-pyridinamine;
4-methoxy-N-[1-[(5-methyl-2-pyrazinyl)carbonyl]-4-piperidinyl]-2-pyridinamine;
N-[1-[4-(aminomethyl)benzoyl]-4-piperidinyl]-4-methoxy-2-pyridinamine;
4-methoxy-N-[1-(4-pyridinylcarbonyl)-4-piperidinyl]-2-pyridinamine;
N-[1-(3-amino-4-chlorobenzoyl)-4-piperidinyl]-4-methoxy-2-pyridinamine;
N-[1-(4-cyanobenzoyl)-4-piperidinyl]-4-chloro-2-pyridinamine;
4-cyano-N-[3-[(4-methyl-2-pyridinyl)amino]propyl]benzamide;
4-cyano-N-[3-[(4-methoxy-2-pyridinyl)amino]propyl]benzamide;
N-[1-(4-chlorobenzoyl)-4-methyl-4-piperidinyl]-4-methoxy-2-pyridinamine;
or a pharmaceutically acceptable salt, enantiomer or tautomer thereof.

8. A compound of formula (I), according to any one of Claims 1 to 7, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, for use as a medicament.

9. A pharmaceutical composition comprising a compound of formula (I) according to any one of Claims 1 to 7, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

10. The use of a compound of formula (I) according to any one of Claims 1 to 7, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, in the manufacture of a medicament for the treatment or prophylaxis of human diseases or conditions in which inhibition of nitric oxide synthase activity is beneficial.

11. The use as claimed in Claim 10 wherein it is predominantly inducible nitric oxide synthase that is inhibited.

12. The use of a compound of formula (I) as defined in any one of Claims 1 to 7, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, in the manufacture of a medicament, for the treatment or prophylaxis of inflammatory diseases.

13. The use as claimed in Claim 12 wherein the disease is inflammatory bowel disease.

14. The use as claimed in Claim 12 wherein the disease is rheumatoid arthritis.

15. The use as claimed in Claim 12 wherein the disease is osteoarthritis.

16. The use of a compound of formula (I) as defined in any one of Claims 1 to 7, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, in the manufacture of a medicament, for the treatment or prophylaxis of pain.

17. The use of a compound of formula (I) as defined in any one of Claims 1 to 7, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, in combination with a

COX-2 inhibitor, in the manufacture of a medicament, for the treatment or prophylaxis of inflammatory diseases.

18. A method of treating, or reducing the risk of, human diseases or conditions in which inhibition of nitric oxide synthase activity is beneficial which comprises administering a therapeutically effective amount of a compound of formula (I), as defined in any one of Claims 1 to 7, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, to a person suffering from, or at increased risk of, such diseases or conditions.

19. A method of treatment according to Claim 18 in which it is predominantly inducible nitric oxide synthase that is inhibited.

20. A method of treating, or reducing the risk of, inflammatory disease in a person suffering from, or at risk of, said disease, wherein the method comprises administering to the person a therapeutically effective amount of a compound of formula (I), as defined in any one of Claims 1 to 7, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof.

21. The method of treatment as claimed in Claim 20 wherein the disease is inflammatory bowel disease.

22. The method of treatment as claimed in Claim 20 wherein the disease is rheumatoid arthritis.

23. The method of treatment as claimed in Claim 20 wherein the disease is osteoarthritis.

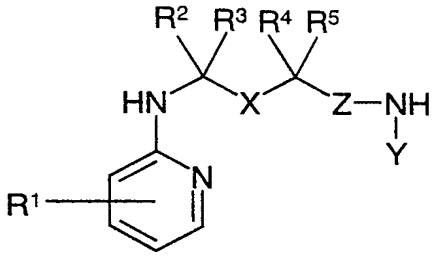
24. A method of treating, or reducing the risk of, pain in a person suffering from, or at risk of, said condition, wherein the method comprises administering to the person a therapeutically effective amount of a compound of formula (I), as defined in any one of Claims 1 to 7, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof.

25. A method of treating, or reducing the risk of, inflammatory disease in a person suffering from, or at risk of, said disease, wherein the method comprises administering to the person a

therapeutically effective amount of a combination of a compound of formula (I), as defined in any one of Claims 1 to 7, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, with a COX-2 inhibitor.

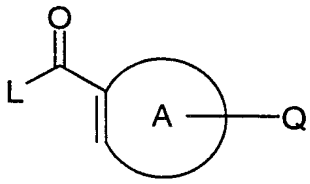
26. A process for the preparation of a compound of formula (I), as defined in any one of Claims 1 to 7, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, wherein the process comprises:

(a) preparing a compound of formula (I) by reaction of a compound of formula (II)



(II)

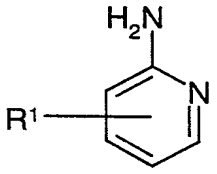
wherein
R^1, R^2, R^3, R^4, R^5, X, Y and Z are as defined in Claim 1
with an acyl derivative of formula (III)



(III)

wherein
Q and A are as defined in Claim 1 and L represents a leaving group;

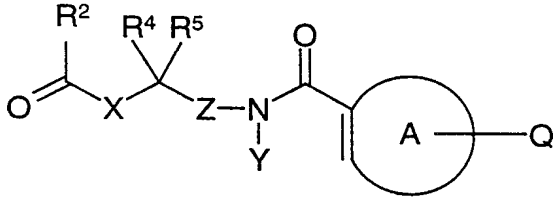
or (b) preparing a compound of formula (I) by reaction of a compound of formula (IV)



(IV)

wherein R^1 is as defined in Claim 1

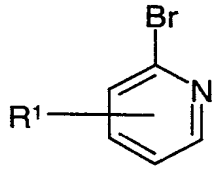
with a compound of formula (V)



(V)

wherein R^2, R^4, $R^{5,}$ A, Q, X, Y and Z are as defined in Claim 1;

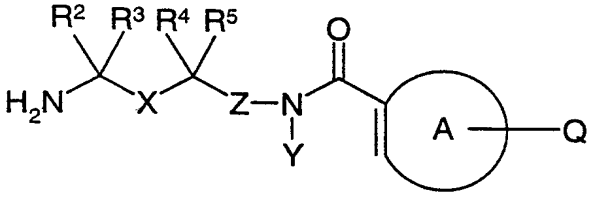
or (c) preparing a compound of formula (I) by reaction of a compound of formula (VI)



(VI)

wherein R^1 is as defined in Claim 1,

with a compound of formula (VII)



(VII)

wherein R^2, R^3, R^4, R^5, A, Q, X, Y and Z are as defined in Claim 1;

and where desired or necessary converting the resultant compound of formula (I), or another salt thereof, into a pharmaceutically acceptable salt thereof, or *vice versa*, and where desired converting the resultant compound of formula (I) into an optical isomer thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/01988

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 401/12, C07D 405/14, A61K 31/445
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9618617 A1 (MERCK & CO., INC.), 20 June 1996 (20.06.96) --	1-17,26
A	EP 0870765 A1 (ZERIA PHARMACEUTICAL CO., LTD.), 14 October 1998 (14.10.98) --	1-17,26
A	WO 9724124 A1 (SMITHKLINE BEECHAM CORPORATION), 10 July 1997 (10.07.97) --	1-17,26
A	WO 9737655 A1 (MERCK & CO., INC.), 16 October 1997 (16.10.97) --	1-17,26

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 March 2000	30 -03- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/01988

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9618628 A1 (THE UPJOHN COMPANY), 20 June 1996 (20.06.96)	1-17,26

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/01988

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 18-25
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy, see rule 39.1.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.
PCT/SE 99/01988

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9618617 A1	20/06/96	AU 4515896 A	03/07/96
EP 0870765 A1	14/10/98	AU 699008 B	19/11/98
		AU 5702496 A	29/11/96
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		CA 2219747 A	21/11/96
		CN 1184471 A	10/06/98
		WO 9636619 A	21/11/96
WO 9724124 A1	10/07/97	AU 1295597 A	28/07/97
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		EP 0906103 A	07/04/99
		IL 125030 D	00/00/00
		NO 983001 A	26/08/98
		PL 327626 A	21/12/98
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		CA 2251017 A	16/10/97
		EP 0901373 A	17/03/99
		GB 9610996 D	00/00/00
		US 5925655 A	20/07/99
WO 9618628 A1	20/06/96	AU 4151696 A	03/07/96
		EP 0797576 A	01/10/97
		IL 116310 D	00/00/00
		JP 10510530 T	13/10/98
		US 5866589 A	02/02/99